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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/349,177	12/02/94	GREY H	14137-58-4

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EXAMINER	
SCHWADRON, R	
ART UNIT	PAPER NUMBER
1644	34

DATE MAILED: 05/15/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/349,177	Grey et al.
Examiner	**Art Unit**
Ron Schwadron, Ph.D.	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 8/16/99, 3/7/2000, 6/19/2000 and 3/9/2001

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *128-145* is/are pending in the application.

4a) Of the above, claim(s) 130-136, 138-144 is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 128, 129, 137, 145 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's submission after final filed on 8/16/99 has been entered.

2. Applicant's election of cancer antigen KMADLVGFLV and Pan DR peptide in Paper No. 35 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 130-136,138-144 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 35.

4. Claims 128,129,137,145 are under consideration. Claims 56-127 were cancelled in the amendment filed 3/9/2001.

5. Regarding the applications to which the instant application claims priority as disclosed in page 1, first paragraph, applicant needs to list the filing date of said applications (see MPEP section 201.11) which states that:

"When the nonprovisional application is entitled under 35 U.S.C. 120 to an earlier U.S. effective filing date, a statement such as "This is a division (continuation, continuation - in - part) of Application No. - --, filed - --" should appear as the first sentence of the description, except in the case of design applications where it should appear as set forth in MPEP § 1503.01.".

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 128,129,137,145 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A) There is no support in the specification as originally filed for a peptide "wherein said peptide comprises an epitope of 8-11 amino acids" with the motif recited in claim 128. The specification discloses a motif for a 9mer peptide (see original claims 1 and 2 and page 3), wherein specific residues are found at positions 2 and 9. The specification discloses a motif for a 10mer peptide (see original claim 11), wherein specific residues are found at positions 2 and 10. However, the specification does not disclose 8-mer or 11-mer peptides with said motif. For example, there is no disclose in the specification of an 8-mer with V/A/T at position 2 from the amino terminus, with the amino acids at the carboxy terminus as per recited in the claim (eg. the specification discloses amino acids at position 2 or 9 in relation to a 9mer or 10mer, not an 8mer or 11mer). The specification is limited to a description of the 9mer/10mer motif wherein it is specified in relation to HLA-A2.1 binding peptides. The instant claims to not recite that the motif is solely in relation to HLA-A2.1 binding peptides. Furthermore, there is no disclosure in the specification as originally filed of the particular subsets of residues recited at the amino acid terminus/carboxy terminus (eg. they are a "range within a range"). There is also disclosure in the specification as originally filed of the limitation "epitope" as recited in the claims. There is no support in the specification as originally filed for the claimed invention (it constitutes new matter).

B) There is no support in the specification as originally filed for the recitation of "Pan DR" epitope in claim 128. There is no support in the specification as originally filed for the claimed invention (it constitutes new matter).

8. Claims 128,129,137,145 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

The specification is not enabling for the claimed composition wherein said peptides are "immunogenic". The specification discloses that an immunogenic peptide is "a peptide which

comprises an allele-specific motif such that the peptide will bind an MHC molecule and induce a CTL response" (page 3, last paragraph, continued on page 4). The specification provides no evidence that the peptides recited in the claims are immunogenic. The specification provides no evidence that the binding data disclosed in the specification in Table 3 establishes that the peptides disclosed in said Tables are actually immunogenic (eg. capable of stimulating a T cell response). It would require undue experimentation to determine which of the billions of peptides recited in the claims are immunogenic and which are not. Celis et al. teach that in order to establish whether a peptide is immunogenic said peptide needs to be tested in assays that actually establish that a peptide is immunogenic (eg. CTL assay, etc.). Celis et al. teach that:

"In addition to MHC binding, other factors such as antigen processing, peptide transport and the composition of the T-cell receptor repertoire could determine whether any of these peptides can function as effective CTL antigens.".

No such data is disclosed in the specification with regards to peptides that are disclosed in Table 3 of the specification. Rammensee et al. teach that "MHC/peptide binding assays have a history of leading to obsolete results" (see page 182, first column). Rammensee et al. teach problems with interpreting data derived from said assays (see page 182, first column). Ochoa-Garay et al. teach that "In summary, the results in this report indicate that the immunogenicity of a peptide cannot always be predicted from its affinity for class I or the presence of class I binding motifs. In addition, our data show that variables such as CTL precursor frequency, peptide hydrophobicity and stability can influence the in vitro induction of CTL responses."(page 279, last sentence continued on page 280). It would require undue experimentation to determine which peptides recited in the claims and encompassed by the formulas recited in the claims are actually immunogenic and which are not. While claim 128 recites that the claimed peptide is immunogenic, it would require undue experimentation to determine which of the trillions of peptides encompassed by the claimed invention are " immunogenic" and which are not. Karin et al. teach that a single substitution in an amino acid, wherein said amino acid plays no role in MHC binding can completely abrogate the immunogenicity of an otherwise immunogenic peptide (see Summary and Table 1). Thus, Karin et al. establish that amino acids not recited in the claimed peptide (eg. amino acids not involved in MHC binding of a peptide) will play a pivotal role in determining whether the peptide recited in the claims is immunogenic. Karin et al. also establish that is unpredictable in the absence of empirical data whether a particular peptide which binds MHC will be immunogenic based on knowledge of whether the peptide has

a particular MHC binding motif because amino acids outside of the MHC binding motif are a critical determining factor with regards to whether a particular peptide is immunogenic. Undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification. See In re Wands 8 USPQ2d 1400(CAFC 1988).

In addition, regarding the use of the claimed invention to treat human disease in vivo, the specification does not disclose how to use the instant invention for the treatment of cancer in vivo in humans. The specification discloses that the claimed pharmaceutical composition is used for the treatment of cancer in humans. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass a pharmaceutical composition for the treatment of cancer in vivo in humans. The state of the art is such that is unpredictable in the absence of appropriate evidence whether the claimed compositions can be used for treatment of cancer in vivo in humans. The specification discloses no working examples with regards to the use of the instant invention for the treatment of disease in vivo in humans.

It would be unpredictable whether the claimed pharmaceutical composition could be used to treat human disease for the same reasons that it is unpredictable whether the claimed peptides are immunogenic. In addition, Boon teaches that it is unclear whether tumor derived peptides can be used to treat human cancer. Boon discloses that a variety of potential problems exist that could prevent therapeutic application of tumor peptide vaccines in humans (eg. loss of tumor antigens and/or MHC expression by variant tumors in vivo can result in tumors which are refractory to killing by cytotoxic cells (see page 178, second column, second paragraph)). Furthermore, the aforementioned tumor antigens already occur in patients, yet are insufficient to render an antitumor response in vivo. Undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification. See In re Wands 8 USPQ2d 1400(CAFC 1988).

9. Claims 128,129,137,145 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 128 and 137 are indefinite in the recitation of "at the carboxy terminus" because it is unclear what this means or encompasses. It is unclear whether this refers to the last amino acid of the peptide recited in the claim or any position that is near the carboxyl terminus.

10. Regarding the application of prior art, for the same reasons that the claimed inventions constitute new matter, the claims are not entitled to priority to the various parent applications to which priority is claimed.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 128,129,137 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boon et al. (US Patent 5,342,774) in view of Sette et al. (US Patent 5,736,142).

Boon et al. teach a tumor antigen derived peptide encompassed by the first peptide recited in claims 128 and 137 wherein said peptide is 15 amino acids and immunogenic (see column 23). Boon et al. do not teach that the peptide is conjugated to a Pan DR epitope peptide. Sette et al. teach Pan DR epitopes and use of said epitopes to enhance CTL responses (see abstract). Sette et al. teach such peptides (see column 6, penultimate paragraph). Sette et al. teach that the Pan DR epitope is conjugated to the CTL peptide (see column 10). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Boon et al. teach the claimed invention except for use of Pan DR peptides, while Sette et al. teach Pan DR peptides and use of said epitopes to enhance CTL responses. One of ordinary skill in the art would have been motivated to do the aforementioned because Sette et al. teach that Pan DR epitopes can be used as a potent immunogen and stimulates responses from a broad pattern of different DR alleles (see column 2, second paragraph). Said conjugate could be used in in vitro assays or animal models to study the potential role of said peptide in tumor rejection. Regarding the limitation pharmaceutical composition, the instant rejection renders obvious the peptide recited in the instant recitation. Regarding the application of prior art, the recitation of an intended use carries no patentable weight in this product claim.

13. Claims 128,129,137 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheever et al. (US Patent 6,075,122) in view of Sette et al. (US Patent 5,736,142).

Cheever et al. teach a tumor antigen derived peptide encompassed by the first peptide recited in claims 128 and 137 wherein said peptide is 10 amino acids and immunogenic (VMAGVGSPYV, see column 12). Cheever et al. do not teach that the peptide is conjugated to a Pan DR epitope peptide. Sette et al. teach Pan DR epitopes and use of said epitopes to enhance CTL responses (see abstract). Sette et al. teach such peptides (see column 6, penultimate paragraph). Sette et al. teach that the Pan DR epitope is conjugated to the CTL peptide (see column 10). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Cheever et al. teach the claimed invention except for use of Pan DR peptides, while Sette et al. teach Pan DR peptides and use of said epitopes to enhance CTL responses. One of ordinary skill in the art would have been motivated to do the aforementioned because Sette et al. teach that Pan DR epitopes can be used as a potent immunogen and stimulates responses from a broad pattern of different DR alleles (see column 2, second paragraph). Said conjugate could be used in in in vitro assays or animal models to study the potential role of said peptide in tumor rejection. Regarding the limitation pharmaceutical composition, the instant rejection renders obvious the peptide recited in the instant recitation. Regarding the application of prior art, the recitation of an intended use carries no patentable weight in this product claim.

14. Claims 128,129,137 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kubo et al. (US Patent 6,037,135) in view of Sette et al. (US Patent 5,736,142).

Kubo et al. teach a tumor antigen derived peptide encompassed by the first peptide recited in claims 128 and 137 wherein said peptide is 10 amino acids and immunogenic (RALAETSYVK, see Table 24). Kubo et al. do not teach that the peptide is conjugated to a Pan DR epitope peptide. Sette et al. teach Pan DR epitopes and use of said epitopes to enhance CTL responses (see abstract). Sette et al. teach such peptides (see column 6, penultimate paragraph). Sette et al. teach that the Pan DR epitope is conjugated to the CTL peptide (see column 10). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Kubo et al. teach the claimed invention except for use of Pan DR peptides, while Sette et al. teach Pan DR peptides and use of said epitopes to enhance CTL responses. One of ordinary skill in the art would have been motivated to do the aforementioned because Sette et al. teach that Pan DR epitopes can be used as a potent immunogen and stimulates responses from a broad pattern of different DR alleles (see column 2,

second paragraph). Said conjugate could be used in in vitro assays or animal models to study the potential role of said peptide in tumor rejection. Regarding the limitation pharmaceutical composition, the instant rejection renders obvious the peptide recited in the instant recitation. Regarding the application of prior art, the recitation of an intended use carries no patentable weight in this product claim.

15. No claim is allowed.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 1600 at (703) 308-4242.

17. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Monday through Thursday from 7:30 to 6:00. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ms Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

RONALD B. SCHWADRON
PRIMARY EXAMINER
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Art Unit 1644